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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/750,315	BERLIN ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-23 and 36-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-23 and 36-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 19 April 2007 in which claims 18, 23, 36, and 40 were amended, claims 1-17 and 24-35 were canceled, and new claims 42-52 were added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 112, first paragraph, are withdrawn in view of the amendments. However, new rejections under 35 U.S.C. 112, first paragraph necessitated by the amendments are presented below.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments. However, new rejections under 35 U.S.C. 112, first paragraph necessitated by the amendments are presented below.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 18-23 and 36-52 are under prosecution.

Petition

2. The Request for Withdrawal as Attorney or Agent and Change of Correspondence Address filed 23 March 2007 is acknowledged and has been entered.

Claim Rejections - 35 USC § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 23 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This is a new matter rejection**. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 23 and 40 each recite "a mesh inside the channel" in lines 1-2 of each of the claims. However, the specification does not teach a mesh inside the inlet channel. Paragraph 19 on page 4 of the specification teaches nucleotides flowing through the chamber into the channel, which can include a mesh. Because the nucleotides have already flowed through the chamber, the mesh is clearly in the outlet channel. Paragraph 82 on page 20 of the specification teaches a mesh in the channel, but does not specifically teach the mesh in either an inlet or outlet channel. Paragraph 99 on page 26 of the specification also teaches a mesh in the channel, but does not specifically teach the mesh in either an inlet or outlet channel. Thus, while paragraph 19 supports a mesh in the outlet channel, the specification does not provide support for a mesh in the inlet channel. Applicant has not indicated where support for this amendment can be found in the specification. Thus, the inclusion of a "mesh inside the channel" encompasses an embodiment wherein the mesh is inside the inlet channel, which constitutes new matter.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 23, 40, 42, and 46-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23 and 40 are each in definite in the recitation "the mesh SERS active metal nanoparticles" in line 2 of each of claims 23 and 40. It is unclear if the "mesh SERS active metal nanoparticles" is a

recitation of two distinct structures, as suggested by line 1 of each of the claims in view of claims 21 and 36, or if the mesh and nanoparticles are somehow attached to one another. In addition, the recitation "the mesh SERS active metal nanoparticles" lacks antecedent basis because none of the previous claims recites "mesh SERS active metal nanoparticles." It suggested the claims be amended to reflect proper antecedent basis and to clearly indicate which structure (i.e., the mesh or the nanoparticles) is required to comprise the recited metals.

Claims 42 and 46 are each indefinite in the recitation "each Raman detection unit" in line 1 of each of claims 42 and 46. The recitation "each Raman detection unit" is indefinite because independent claims 41 and 45 each have only 1 Raman detection unit, whereas the phrase "each Raman detection unit" indicates more than one Raman detection unit. It is suggested that the word "each" be deleted from each of the claims.

Claim 47 is indefinite in the recitation "the concentrations of nucleotides is measured by Raman spectroscopy as they flow through the inlet channel and outlet channel" at the end of claim 47. It is unclear how the concentration are measured at the inlet channel because the apparatus of independent claim 45 only has a Raman unit coupled only to the outlet channel; thus, no measurement is possible at the inlet channel.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly

owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 18-26 and 36-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shipwash (U.S. Patent Application Publication No. US 2002/0058273 A1, published 16 May 2002) in view of Natan (U.S. Patent Application Publication No. US 2002/0142480 A1, published 3 October 2002).

It is noted that a prior art reference is considered as a whole and for all it stands for. Thus, while the rejections listed below present a modified interpretation of the teachings of Shipwash et al in view of Natan solely for the purpose of clarity, the rejections of the claims are maintained for the reasons of record. Thus, the claims are still obvious over the prior art of record as discussed below.

Regarding claim 18, Shipwash teaches an apparatus. In a single exemplary embodiment, Shipwash teaches a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface; namely, a mixing channel, which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraphs 0066 and 0255). The apparatus of Shipwash further comprises an inlet channel in fluid communication with the reaction chamber; namely, Figure 11, wherein the inlet channel comprises the channel having the digestion chamber (Figure 11). Shipwash also teaches the apparatus comprises an outlet channel in fluid communication with the reaction chamber; namely, Figure 11, wherein the outlet channel is end of one of the reaction channels (paragraphs 0482-0484). The reaction channels are outlet channels because they are at the end of the device and follow the reaction chamber.

Shipwash also teaches a first Raman detection unit operably coupled to the inlet channel; namely, an optical detector is integrated onto the inlet digestion chamber (paragraph 0484), wherein Raman

Spectroscopy is used (paragraph 0174); thus, the first optical detector is a Raman detection unit. Shipwash also teaches a second Raman detection unit operably coupled to the outlet channel; namely, a second detector is coupled to the outlet (i.e., reaction) channels of Figure 11. The second detector is a Raman spectrophotometer and Raman Spectroscopy is used (paragraphs 0224 and 0174). The first and second detectors are therefore distinct and separate from the reaction chamber and are positioned before and after the reaction chamber (i.e., mixing channel).

Shipwash also teaches detection of oligonucleotides; namely. AMP is detected upon binding to an oligonucleotide aptamer (paragraph 0155).

Shipwash does not teach the Raman detection units configured for surface enhanced Raman spectroscopy.

However, Natan teaches the Raman detection units configured for surface enhanced Raman spectroscopy (paragraph 0042) of nucleic acids (paragraph 0059) with the added advantage that surface enhanced Raman spectroscopy allows detection of molecules (i.e., nucleic acids) attached to the surface of a single metal nanoparticle in multiplexed assay formats (paragraph 0006), thereby increasing the sensitivity of the detection and increasing the number of different molecules detectable in a single assay.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising two Raman detection units of Shipwash with detectors of surface enhanced Raman spectroscopy as taught by Natan with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of allowing detection of nucleic acid molecules attached to the surface of a single metal nanoparticle in multiplexed assay formats, thereby increasing the sensitivity of the detection and increasing the number of different molecules detectable in a single assay, as explicitly taught by Natan (paragraph 0006).

Regarding claim 19, the apparatus of claim 18 is discussed above. Shipwash also teaches each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level; namely,

single molecule detection is performed (paragraph 0168). Nucleotides are molecules; thus, because single molecule detection is performed, and because nucleotides are molecules, Shipwash teaches at least one nucleotide is detected at the single molecule level.

Regarding claim 20, the apparatus of claim 18 is discussed above. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the inlet channel and the outlet channel; namely, the system detects concentration (paragraph 0170) and uses Raman spectroscopy (paragraph 0174).

In addition, the courts have held that "while features of an apparatus may be recited either structurally or functionally, claims directed to an apparatus must be distinguished from the prior art in terms of structure rather than function." *In re Schreiber*, 128 F.3d 1473, 1477-78, 44 USPQ2d 1429, 1431-32 (Fed. Cir. 1997). In addition, "[A]pparatus claims cover what a device *is*, not what a device *does*." *Hewlett-Packard Co. v. Bausch &Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990) (emphasis in original). Therefore, the various uses recited in claim 20 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 18. Because Shipwash in view of Natan teaches the structural elements of claim 18, claim 20 is obvious over the prior art.

Regarding claim 21, the apparatus of claim 18 is discussed above. Shipwash teaches nucleic acids are on metal particles in channels (paragraph 0043), which is interpreted as being in the inlet and outlet channels. Shipwash does not explicitly teach surface enhanced Raman spectroscopy active particles.

However, Natan teaches surface enhanced Raman spectroscopy active particles; namely, SERS active composite nanoparticles, which have the added advantages of being stabilized against decomposition of the analyte in solvent and air, chemically inert, and easily centrifuged and redispersed without loss of SERS activity (paragraphs 0007-0009).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising two Raman detection units of Shipwash with the surface enhanced Raman spectroscopy active particles as taught by Natan with a

reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of having particles that are stabilized against decomposition of the analyte in solvent and air, chemically inert, and easily centrifuged and redispersed without loss of SERS activity as explicitly taught by Natan (paragraph 0007-0009).

Regarding claim 22, the apparatus of claim 18 is discussed above. Shipwash also teaches the inlet channel and outlet channel diameter is between about 100 and about 200 micrometers in diameter (paragraph 0210).

Regarding claim 23, the apparatus of claim 18 is discussed above. While Shipwash also teaches the apparatus further comprises a mesh in the form of filters and grids that retain nanoparticles in the channels of the apparatus (paragraphs 0167 and 0270), Shipwash is silent with respect to the materials used for the mesh and SERS active nanoparticles.

However, Natan teaches SERS sandwich nanoparticles (i.e., SSNs; paragraph 0020 and Figure 1) made of gold (paragraph 0047) wherein the SSNs interlock to form a mesh and having the added advantage that the mesh allows the overall shape of the SSNs, and thus the mesh, to be chosen (paragraph 0031). Natan also teaches that the use of gold allows ready chemical enhancement of the SERS nanoparticles (paragraph 0029).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising the mesh having retained nanoparticles of Shipwash with meshed gold nanoparticles as taught by Natan with a reasonable expectation of success. The retention of the meshed nanoparticles of Natan on the mesh of Shipwash would result in a mesh inside the channel comprising surface enhanced Raman spectroscopy active gold nanoparticles. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of having a mesh with a

controlled overall shape as well as nanoparticles that are readily chemically enhanced as explicitly taught by Natan (paragraphs 0031 and 0029).

Regarding claim 36, Shipwash teaches an apparatus. Shipwash teaches an apparatus. In a single exemplary embodiment, Shipwash teaches a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface; namely, a mixing channel, which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraphs 0066 and 0255). The apparatus of Shipwash further comprises an inlet channel in fluid communication with the reaction chamber; namely, Figure 11, wherein the inlet channel comprises the channel having the digestion chamber (Figure 11). Shipwash also teaches the apparatus comprises an outlet channel in fluid communication with the reaction chamber; namely, Figure 11, wherein the outlet channel is end of one of the reaction channels (paragraphs 0482-0484). The reaction channels are outlet channels because they are at the end of the device and follow the reaction chamber.

Shipwash also teaches a first Raman detection unit operably coupled to the inlet channel; namely, an optical detector is integrated onto the inlet digestion chamber (paragraph 0484), wherein Raman Spectroscopy is used (paragraph 0174); thus, the first optical detector is a Raman detection unit. Shipwash also teaches a second Raman detection unit operably coupled to the outlet channel; namely, a second detector is coupled to the outlet (i.e., reaction) channels of Figure 11. The second detector is a Raman spectrophotometer and Raman Spectroscopy is used; paragraphs 0224 and 0174). The first and second detectors are therefore distinct and separate from the reaction chamber and are positioned before and after the reaction chamber (i.e., mixing channel). Shipwash further teaches nucleic acids are on metal particles in channels (paragraph 0043), which is interpreted as being in the inlet and outlet channels.

Shipwash also teaches detection of oligonucleotides; namely. AMP is detected upon binding to an oligonucleotide aptamer (paragraph 0155).

Shipwash does not teach Raman detection units configured for surface enhanced Raman spectroscopy, nor does Shipwash does not explicitly teach surface enhanced Raman spectroscopy active particles.

However, Natan teaches the detectors configured to perform surface enhanced Raman spectroscopy (paragraph 0042) of nucleic acids (paragraph 0059) with the added advantage that surface enhanced Raman spectroscopy allows detection of molecules attached to the surface of a single metal nanoparticle in multiplexed assay formats (paragraph 0006) thereby increasing the sensitivity of the detection and increasing the number of different molecules detectable in a single assay. Natan also teaches surface enhanced Raman spectroscopy active particles; namely, SERS active composite nanoparticles, which have the additional added advantages of being stabilized against decomposition of the analyte in solvent and air, chemically inert, and easily centrifuged and redispersed without loss of SERS activity (paragraphs 0007-0009).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising two Raman detection units and nanoparticles of Shipwash with detectors of surface enhanced Raman spectroscopy and the surface enhanced Raman spectroscopy active particles as taught by Natan with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of allowing detection of nucleic acid molecules attached to the surface of a single metal nanoparticle in multiplexed assay formats thereby increasing the sensitivity of the detection and increasing the number of different molecules detectable in a single assay, as well as the additional added advantage of providing particles that are stabilized against decomposition of the analyte in solvent and air, chemically inert, and easily centrifuged and redispersed without loss of SERS activity as explicitly taught by Natan (paragraphs 0006-0009).

Regarding claim 37, the apparatus of claim 36 is discussed above. Shipwash also teaches each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level; namely,

single molecule detection is performed (paragraph 0168). Nucleotides are molecules; thus, because single molecule detection is performed, and because nucleotides are molecules, Shipwash teaches at least one nucleotide is detected at the single molecule level.

Regarding claim 38, the apparatus of claim 36 is discussed above. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the inlet channel and the outlet channel; namely, the system detects concentration (paragraph 0170) and uses Raman spectroscopy (paragraph 0174).

In addition, as noted above, the courts have held that while features of an apparatus may be recited either structurally or functionally, claims directed to an apparatus must be distinguished from the prior art in terms of structure rather than function. Therefore, the various uses recited in claim 38 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 36. Because Shipwash in view of Natan teaches the structural elements of claim 36, claim 38 is obvious over the prior art.

Regarding claim 39, the apparatus of claim 36 is discussed above. Shipwash also teaches the inlet channel and outlet channel diameter is between about 100 and about 200 micrometers in diameter (paragraph 0210).

Regarding claim 40, the apparatus of claim 36 is discussed above. While Shipwash also teaches the apparatus further comprises a mesh in the form of filter and grids that retain nanoparticles in the channels of the apparatus (paragraphs 0167 and 0270), Shipwash is silent with respect to the materials used for the mesh and SERS active nanoparticles.

However, Natan teaches SERS sandwich nanoparticles (i.e., SSNs; paragraph 0020 and Figure 1) made of gold (paragraph 0047) wherein the SSNs interlock to form a mesh and having the added advantage that the mesh allows the overall shape of the SSNs, and thus the mesh, to be chosen (paragraph 0031). Natan also teaches that the use of gold allows ready chemical enhancement of the SERS nanoparticles (paragraph 0029).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising the mesh having retained nanoparticles of Shipwash with meshed gold nanoparticles as taught by Natan with a reasonable expectation of success. The retention of the meshed nanoparticles of Natan on the mesh of Shipwash would result in a mesh inside the channel comprising surface enhanced Raman spectroscopy active gold nanoparticles. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of a mesh with a controlled overall shape as well as the additional added advantage of having nanoparticles that are readily chemically enhanced as explicitly taught by Natan (paragraphs 0031 and 0029).

Regarding claim 41, Shipwash teaches an apparatus. In a single exemplary embodiment, Shipwash teaches a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface; namely, a mixing channel, which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraphs 0066 and 0255). The apparatus of Shipwash further comprises an inlet channel in fluid communication with the reaction chamber; namely, Figure 11, wherein the inlet channel comprises the channel having the digestion chamber (Figure 11). Shipwash also teaches the apparatus comprises an outlet channel in fluid communication with the reaction chamber; namely, Figure 11, wherein the outlet channel is end of one of the reaction channels (paragraphs 0482-0484). The reaction channels are outlet channels because they are at the end of the device and follow the reaction chamber.

Shipwash also teaches a Raman detection unit operably coupled to the outlet channel; namely, a detector is coupled to the outlet (i.e., reaction) channels of Figure 11. The detector is a Raman spectrophotometer and Raman Spectroscopy is used (paragraphs 0224 and 0174). The Raman detection unit is therefore distinct and separate from the reaction chamber and is positioned after the reaction chamber (i.e., mixing channel).

Shipwash also teaches detection of oligonucleotides; namely. AMP is detected upon binding to an oligonucleotide aptamer (paragraph 0155).

Shipwash does not teach the Raman detection units configured for surface enhanced Raman spectroscopy.

However, Natan teaches the Raman detection units configured for surface enhanced Raman spectroscopy (paragraph 0042) nucleic acids (paragraph 0059) with the added advantage that surface enhanced Raman spectroscopy allows detection of nucleic acid molecules attached to the surface of a single metal nanoparticle in multiplexed assay formats (paragraph 0006), thereby increasing the sensitivity of the detection and increasing the number of different molecules detectable in a single assay.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising two Raman detection units of Shipwash with detectors of surface enhanced Raman spectroscopy as taught by Natan with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of allowing detection of nucleic acid molecules attached to the surface of a single metal nanoparticle in multiplexed assay formats, thereby increasing the sensitivity of the detection and increasing the number of different molecules detectable in a single assay, as explicitly taught by Natan (paragraph 0006).

Regarding claim 42, the apparatus of claim 41 is discussed above. Shipwash also teaches each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level; namely, single molecule detection is performed (paragraph 0168). Nucleotides are molecules; thus, because single molecule detection is performed, and because nucleotides are molecules, Shipwash teaches at least one nucleotide is detected at the single molecule level.

Regarding claim 43, the apparatus of claim 41 is discussed above. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the inlet

channel and the outlet channel; namely, the system detects concentration (paragraph 0170) and uses Raman spectroscopy (paragraph 0174).

In addition, as noted above, the courts have held that while features of an apparatus may be recited either structurally or functionally, claims directed to an apparatus must be distinguished from the prior art in terms of structure rather than function. Therefore, the various uses recited in claim 38 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 36. Because Shipwash in view of Natan teaches the structural elements of claim 36, claim 38 is obvious over the prior art.

Regarding claim 44, the apparatus of claim 41 is discussed above. Shipwash also teaches the inlet channel and outlet channel diameter is between about 100 and about 200 micrometers in diameter (paragraph 0210).

Regarding claim 45, Shipwash teaches an apparatus. In a single exemplary embodiment, Shipwash teaches a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface; namely, a mixing channel, which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraphs 0066 and 0255). The apparatus of Shipwash further comprises an inlet channel in fluid communication with the reaction chamber; namely, Figure 11, wherein the inlet channel comprises the channel having the digestion chamber (Figure 11). Shipwash also teaches the apparatus comprises an outlet channel in fluid communication with the reaction chamber; namely, Figure 11, wherein the outlet channel is end of one of the reaction channels (paragraphs 0482-0484). The reaction channels are outlet channels because they are at the end of the device and follow the reaction chamber. Shipwash further teaches nucleic acids are on metal particles in channels (paragraph 0043), which is interpreted as being in the inlet and outlet channels.

Shipwash also teaches a Raman detection unit operably coupled to the outlet channel; namely, a detector is coupled to the outlet (i.e., reaction) channels of Figure 11. The detector is a Raman

spectrophotometer and Raman Spectroscopy is used (paragraphs 0224 and 0174). The Raman detection unit is therefore distinct and separate from the reaction chamber and is positioned after the reaction chamber (i.e., mixing channel).

Shipwash also teaches detection of oligonucleotides; namely. AMP is detected upon binding to an oligonucleotide aptamer (paragraph 0155).

Shipwash does not teach Raman detection units configured for surface enhanced Raman spectroscopy, nor does Shipwash does not explicitly teach surface enhanced Raman spectroscopy active particles.

However, Natan teaches the detectors configured to perform surface enhanced Raman spectroscopy (paragraph 0042) of nucleic acids (paragraph 0059) with the added advantage that surface enhanced Raman spectroscopy allows detection of molecules attached to the surface of a single metal nanoparticle in multiplexed assay formats (paragraph 0006) thereby increasing the sensitivity of the detection and increasing the number of different molecules detectable in a single assay. Natan also teaches surface enhanced Raman spectroscopy active particles; namely, SERS active composite nanoparticles, which have the additional added advantages of being stabilized against decomposition of the analyte in solvent and air, chemically inert, and easily centrifuged and redispersed without loss of SERS activity (paragraphs 0007-0009).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus comprising two Raman detection units and nanoparticles of Shipwash with detectors of surface enhanced Raman spectroscopy and the surface enhanced Raman spectroscopy active particles as taught by Natan with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of allowing detection of nucleic acid molecules attached to the surface of a single metal nanoparticle in multiplexed assay formats thereby increasing the sensitivity of the detection and increasing the number of different molecules

detectable in a single assay, as well as the additional added advantage of providing particles that are stabilized against decomposition of the analyte in solvent and air, chemically inert, and easily centrifuged and redispersed without loss of SERS activity as explicitly taught by Natan (paragraphs 0006-0009).

Regarding claim 46, the apparatus of claim 45 is discussed above. Shipwash also teaches each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level; namely, single molecule detection is performed (paragraph 0168). Nucleotides are molecules; thus, because single molecule detection is performed, and because nucleotides are molecules, Shipwash teaches at least one nucleotide is detected at the single molecule level.

Regarding claim 47, the apparatus of claim 45 is discussed above. Shipwash also teaches the concentrations of nucleotides are measured by Raman spectroscopy as they flow through the inlet channel and the outlet channel; namely, the system detects concentration (paragraph 0170) and uses Raman spectroscopy (paragraph 0174).

In addition, as noted above, the courts have held that while features of an apparatus may be recited either structurally or functionally, claims directed to an apparatus must be distinguished from the prior art in terms of structure rather than function. Therefore, the various uses recited in claim 38 (e.g., measuring concentration of nucleotides) fail to define additional structural elements to the device of claim 36. Because Shipwash in view of Natan teaches the structural elements of claim 36, claim 38 is obvious over the prior art.

Regarding claim 48, the apparatus of claim 45 is discussed above. Shipwash also teaches the inlet channel and outlet channel diameter is between about 100 and about 200 micrometers in diameter (paragraph 0210).

Response to Arguments

Applicant's arguments filed 19 April 2007 (i.e., the "Remarks") have been fully considered but they are not persuasive for the reason(s) listed below.

A. Applicant argues on page 7 of the Remarks that neither Shipwash nor Natan teaches first and second Raman detectors distinct and separate from the reaction chamber and position before and after the reaction chamber.

However, as noted above, Shipwash teaches a mixing channel, which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraphs 0066 and 0255). Shipwash also teaches a first Raman detection unit operably coupled to the inlet channel; namely, an optical detector is integrated onto the inlet digestion chamber (paragraph 0484), wherein Raman Spectroscopy is used (paragraph 0174); thus, the first optical detector is a Raman detection unit. Shipwash also teaches a second Raman detection unit operably coupled to the outlet channel; namely, a second detector is coupled to the outlet (i.e., reaction) channels of Figure 11. The second detector is a Raman spectrophotometer and Raman Spectroscopy is used; paragraphs 0224 and 0174). The first and second detectors are therefore distinct and separate from the reaction chamber and are positioned before and after the reaction chamber (i.e., mixing channel). Thus, Shipwash teaches the limitations listed above.

B. Applicant further argues on page 8 of the Remarks that Shipwash does not teach the detection units are capable of detecting at least one nucleotide at the single molecule level.

However, as noted above, Shipwash teaches each Raman detection unit is capable of detecting at least one nucleotide at the single molecule level because single molecule detection is performed (paragraph 0168). Nucleotides are molecules; thus, because single molecule detection is performed, and because nucleotides are molecules, Shipwash teaches at least one nucleotide is detected at the single molecule level.

In addition, it is noted that the claims are drawn to Raman detectors "capable of detecting at least one nucleotide at the single molecule level." The phrase "at least" indicates a minimal detection threshold, and therefore encompasses alternative embodiments that detect more than one nucleotide at the single molecule level. These alternative embodiments include, but are not limited to, detectors capable of detecting: one million nucleotides at the single molecule level; one nucleotide at the molecule

level of one mole of molecules; or one million nucleotides at the molecule level of one mole of molecules. Thus, the inclusion of the phrase "at least" encompasses detection sensitivity at virtually any level, and the claim has been given the broadest reasonable interpretation consistent with the specification (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

10. Claims 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shipwash (U.S. Patent Application Publication No. US 2002/0058273 A1, published 16 May 2002) in view of Natan (U.S. Patent Application Publication No. US 2002/0142480 A1, published 3 October 2002) as applied to claims 18, 36, 41, and 45 above, and further in view of French et al (U.S. Patent No. 6,297,018 B1, issued 2 October 2000).

Regarding claim 49-52, the teachings of Shipwash and Natan as applicable to the apparatuses of claim 18, 36, 41, and 45 are discussed above on pages 5-6, 8-10, 12-13, and 13-15 respectively.

While Shipwash teaches microfluidic systems for polymerase chain reactions (i.e., PCR; paragraph 0015), neither Shipwash nor Natan explicitly teaches confinement of the template, a primer, and a polymerase to the reaction chamber.

However, French et al teach chambers for polymerase chain reactions (column 39, lines 30-45) wherein the polymerase is immobilized therein and all of the remaining reagents (i.e., the primers) are stabilized therein (column 11, lines 38-50). The immobilization of the polymerase and stabilization of the remaining reagents in the PCR chamber results in confinement of the template, a primer, and the polymerase in a reaction chamber. French et al further teach the immobilized polymerase and confined reagents have the added advantage of allowing assays to be run simply by adding the template (i.e., sample) and buffer (column 11, lines 38-50), which results in a simplified assay procedure.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the apparatus of Shipwash in view of Natan with the confined reagents as taught by French et al with a reasonable expectation of success. The ordinary artisan

would have been motivated to make such a modification because said modification would have resulted in an apparatus having the added advantage of allowing a simplified assay procedure by allowing assays to be run simply by adding the template and buffer as explicitly taught by French et al (column 11, lines 38-50).

Conclusion

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

13. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert T. Crow
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER